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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/591,185	06/08/00	COOK R	19079-000310

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EXAMINER	
EPPS, J	
ART UNIT	**PAPER NUMBER**
1635	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/591,185	Applicant(s) COOK, RONALD M.	
	Examiner Janet L Epps	Art Unit 1635	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☒ Other: Notice to Comply

DETAILED ACTION

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1635.

Sequence Information

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. See pages 54 and 55 for nucleotide sequences of 10 nucleotides or more that are not listed separately on a Sequence Listing, and have not been assigned an appropriate sequence identifier (SEQ ID NO:).

A complete response to this Office Action requires that Applicants comply with the sequence rules, and that pending rejections be addressed. Any response that does not address all of these issues will be held as non-responsive. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Priority

3. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: Applicants state that the present application is a CIP of provisional application 60/138,376. See MPEP § 201.08

[R-1], which states: An application claiming the benefits of a provisional application under 35 U.S.C. 119(e) should not be called a "continuation-in-part" of the provisional application since the application will have its patent term calculated from its filing date, whereas an application filed under 35 U.S.C. 120, 121, or 365(c) will have its patent term calculated from the date on which the earliest application was filed, provided a specific reference is made to the earlier filed application(s), 35 U.S.C. 154(a)(2) and (a)(3).

Claim Objections

4. Claim 27 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 27 recites wherein Y1 and Y2 are members independently selected from substituted or un-substituted alkyl and substituted or un-substituted heteroalkyl, these terms are defined in claim 26 in the same manner, there is no change in scope.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 3-8, 12, 14-17, 20 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites the term "said molecular energy donor is a fluorophore," in claim 1. There is lack of antecedent basis for this limitation in claim 1.

Claims 4-5 recite "wherein X and Y are both hydrophobic moieties," in claim 1. There is lack of antecedent basis for this limitation in claim 1.

Claim 6 recites "wherein natural nucleic acids" in claim 1. There is lack of antecedent basis for this limitation in claim 1.

Claim 7 recites "said modified nucleic acids are peptide nucleic acids," in claim 1. There is lack of antecedent basis for this limitation in claim 1.

Claim 8 recites the phrase "selected from the group consisting phosphodiesters and modified phosphodiesters." This phrase is vague and indefinite since the phrase lacks an appropriate court defined transitional phrase. This rejection could be obviated if applicants were to amend the claim to recite the phrase "selected from the group consisting of phosphodiesters and modified phosphodiesters."

Claim 12 recites "wherein X and Y are independently attached to members," in claim 1. There is lack of antecedent basis for this limitation in claim 1.

Claims 14-15 are rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting an essential step, such omission does not set forth the method in clear and unambiguous terms. See MPEP § 2172.01. The omitted step of claims 14-15 is a correlation, or recapitulations step at the end of the claim which restates the preamble. Additionally, the instant method lacks the steps required to practice the claimed method to amplify DNA.

Claims 16-17 are rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting an essential step, such omission does not set forth the method in clear and unambiguous terms. See MPEP § 2172.01. The omitted step of claims 16-17 is a correlation, or recapitulation steps at the end of the claim which restates the preamble. Additionally, the instant method lacks the steps required to practice the claimed method to analyzing or quantitating DNA.

Claim 20 defines R2 as having the formula –O-(R11-PEG-Y3-CHOL)-O-, this definition of R2 is unclear since the formula recited in claim 19 defines R2 in the following manner: Nu1-(R2-CHOL)-O-. If R2 as defined in claim 20 was substituted into the structure of claim 19 this would yield the following structure Nu1-(-O-(R11-PEG-Y3-CHOL)-O)-CHOL)-O-, such a structure is difficult to ascertain. It is likely that Applicants intended to define R2 as simply being –R11-PEG-Y3-.

Claim 31 recites "the terms "-R^5-D" and "-R^6Q," these terms are ambiguous since these terms are not properly defined in the instant claim or in claim 1.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-3, 6-11, 13-26 and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al. in view of Manoharan et al. and Gold et al.

The instant claims read on a compound having the formula recited in claim 1 of the instant application, wherein said compound is a modified nucleic acid molecule comprising two cholesterol derivatives linked by a substituted or unsubstituted alkyl or heteroalkyl, and further comprising an electron donor and acceptor attached to both terminal nucleotides or nucleoside by means of a linker moiety, and wherein said compound comprises a hybridization enhancing agent, and further wherein said compound is immobilized on a solid surface. Claims 14-16 read on methods for amplifying, analyzing or quantitating DNA, although these claims are improper or incomplete process claims they are being examined in so far as the prior art reads on the preamble of the claimed methods. Due to the ambiguity with regards to the definition of R2 given in claim 20, for prior art purposes R2 is interpreted as being defined as –R11-PEG-Y3-.

Meade et al. disclose nucleic acid molecules comprising electron donor and electron acceptor moieties covalently bound to the ribose-phosphate backbone of said nucleic acid (col. 5, lines 45-53). Some of the electron donor and acceptor moieties include transitional metal derivatives of imidazole, pyridine, and phenanthroline. Additionally, other organic electron donors and acceptors may be covalently attached to the nucleic acid for use in the invention, these include, but are not limited to, acridine orange, orange, N,N'-dimethyl-2,7-diazapyrenium dichloride (DAP^{2+}), methylviologen, ethidium bromide, quinones such as N,N'-dimethylanthradiisoquinoline dichloride (ADIQ.sup.2+); porphyrins ([meso-tetrakis(N-methyl-x-pyridinium)porphyrin tetrachloride] and subsitituted derivatives of these compounds (col. 9, lines 1-33). The

modified nucleic acid molecules of this invention may include those attached to an immobilized surface such as an electrode (see col. 25, lines 44-67). Additionally, Meade et al. teach that their modified nucleic acid probes may be used in a method of amplifying DNA, wherein the detection of electron transfer after photoinduction would be used as an indication of a successful amplification (col. 12, lines 25-40).

The invention of Meade et al. provides a means to develop novel bioconductors and diagnostic probes (col. 5, lines 27-30). However, Meade et al. do not expressly teach the combination of oligonucleotides comprising both an electron donor and an electron acceptor at either the 5' or 3' terminus and further comprising two internal nucleotides modified with a cholesterol derivative, or a cholesterol-NH-(C=O)-O-PEG group inserted between two phosphate groups of a nucleic acid by means of the PEG linker, nor do they teach the incorporation of hybridization enhancing moieties.

The invention of Manoharan et al. is directed to sequence specific oligonucleotides that include functionalized nucleosides having substituents such as steroids, reporter molecules, reporter enzymes, non-aromatic lipophilic molecules, peptides, or proteins attached via linking groups (col. 1, lines 20-24). The substituents can be attached via a linking group at any of the 3' or the 5' positions of the nucleoside or on the heterocyclic base of the nucleoside or on the inter-nucleotide linkage linking the nucleoside to an adjacent nucleoside (abstract). In certain preferred embodiments of the invention, the substituents comprise a steroid molecule, biotin, a reporter enzyme or a fluorescein dye molecule. In these embodiments, the steroid molecule is selected from the group consisting of cholic acid, deoxycholic acid, dehydrocholic acid,

cortisone, testosterone, cholesterol and digoxigenin with the most preferred steroid molecule being cholic acid (col. 3, lines 41-48). Manoharan et al. teach that a large number of functional groups may incorporated into a linked nucleoside sequence, they further teach that all nucleoside residues in a sequence may be substituted (col. 8, lines 53-65). The compounds of Manoharan et al. may also include those having modified internucleoside linkages, for example those comprising phosphorothioate internucleoside linkages (see example 6, col. 12). Additionally, Manoharan et al. disclose that incorporation of, for example, a 2'-O-methyl, 2'-O-ethyl, 2'-O-propyl, 2'-O-allyl, 2'-O-aminoalkyl or 2'-deoxy-2'-fluoro groups on the nucleosides of an oligonucleotide enhance the hybridization properties of the oligonucleotide (col. 8, lines 8-27). This reference also discloses examples wherein oligonucleotides have cholesterol moieties attached by an amino linker to both the 5'-terminus and the 3' terminus of the oligonucleotide sequence (see col. 12, lines 35-61; and col. 13, lines 14-38), and an oligonucleotide having two internal nucleotides modified with a cholesterol moiety (see col. 17, lines 33-39).

Manoharan et al. provide sequence-specific oligonucleotides having improved transfer and uptake across cellular membranes. Additionally, the oligonucleotides of this invention are useful for research and diagnostic methods and materials for assaying bodily states in animals, especially disease states. However, Manoharan et al. do not expressly teach the linking of cholesterol moieties to a nucleic acid sequence comprising the use of a PEG linker group.

Gold et al. provide methods of derivatizing nucleic acid molecules for the purpose of preparing therapeutic or diagnostic complexes, improving the cellular uptake and the pharmacokinetic properties of nucleic acids (col. 1, lines 13-44). Gold et al. teach nucleic acid molecules derivatized with both a photoreactive group, for example fluorescein and a lipophilic group, such as a cholesterol-NH-(C=O)-O-PEG moiety (see Figure 1B). This reference teaches that a cholesterol group can be introduced at any position in a nucleic acid sequence. In addition, they provide an example of a nucleic acid molecule derivatized with a cholesterol-NH-(C=O)-O-PEG group and observed that this modification retains the same binding affinity for its complementary sequence as the non derivatized nucleic acid molecule (col. 36, lines 20-31).

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to modify the oligonucleotide probes of Meade et al., having an electron donor and an electron acceptor moiety attached to either the 5' or 3' terminus, with the cholesterol modifications taught by either Manoharan et al. or Gold et al., in the synthesis of oligonucleotides according to the instant invention. It would have been obvious because, the prior art discloses electron donor and acceptor modified oligonucleotides and methods for introducing cholesterol modifications into two non-terminal nucleotides of an oligonucleotide wherein the modification may be located at any 2', 3' or 5' positions of a nucleoside (Manoharan et al. see abstract and col. 4, lines 13-22), and further wherein said modification confers enhanced cellular uptake and transfer across cellular membranes to said oligonucleotide. Additionally, the prior art teaches (Gold et al.) that linking a cholesterol moiety between two phosphate residues

of an oligonucleotide by means of a PEG linker would produce an oligonucleotide having enhanced cellular uptake while retaining the same binding affinity as a non-derivatized oligonucleotide. One of ordinary skill in the art would have been motivated to modify the nucleic acid probes of Meade et al. with the modifications of Manoharan et al. and Gold et al. because the modified oligonucleotides of Manoharan et al. and Gold et al. and the nucleic acid probes of Meade et al. are disclosed as useful for the same purposes, particularly for diagnostic purposes, and the modifications of Manoharan et al. and Gold et al. would confer enhanced pharmacokinetic properties to the nucleic acid probes of Meade et al.

Therefore, the invention as a whole would have been *prima facie* obvious at the time the invention was made over Meade et al. in view of Manoharan et al. and Gold et al.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps whose telephone number is 703-308-8883. The examiner can normally be reached on Mondays through Friday, 9:00AM to 6:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps
Patent Examiner
May 2, 2001